

Simultaneous confidence bands for the integrated hazard function

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Abstract

The construction of the simultaneous confidence bands for the integrated hazard function is considered. The Nelson–Aalen estimator is used. The simultaneous confidence bands based on bootstrap methods are presented. Two methods of construction of such confidence bands are proposed. The weird bootstrap method is used for resampling. Simulations are made to compare the actual coverage probability of the bootstrap and the asymptotic simultaneous confidence bands. It is shown that the equal-tailed bootstrap confidence band has the coverage probability closest to the nominal one. We also present application of our confidence bands to the data regarding survival after heart transplant.

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1 Introduction and summary

In biomedical settings, the multiplicative intensity model introduced by Aalen has many applications. This is a model for point processes observed on a fixed time interval for which the stochastic intensity is decomposed into deterministic function $\alpha(t)$ and stochastic process $Y(t)$. The $\alpha(t)$ function may be considered as an individual force of transition at time t and $Y(t)$ as a number at risk just before time t .

In broad terms what makes survival data special is the presence of censored data. To analyze such data by the multiplicative intensity model a general assumption of independent censoring is required, which means that at any time t the survival experience in the future is not statistically altered by censoring and survival experience in the past. The censoring mechanism is modelled by Y process and has not any influence on the α function.

In the survival analysis the most interesting is to estimate the survivor function and the integrated hazard function. In this paper we consider the latter, which is estimated by the Nelson–Aalen estimator. An interpretation of this estimator is difficult without construction of some confidence intervals. From our perspective, the pointwise intervals are not totally satisfactory while one wants to construct confidence region for the whole curve simultaneously for all points.

The construction of the simultaneous confidence bands is difficult since we need the uniform consistency property. However, such confidence bands are badly needed in practical applications. For example, in the works related with ours like in the papers of Cowling, Hall, Phillips ([6]) and Snethlage ([14]) but also in the time series analysis (Leśkow and Wronka [12]) and the nonparametric regression (Loader [13]).

The formula for the asymptotic confidence interval for the Nelson–Aalen estimator is known, however, it is very complicated and does not work well for small samples (see [1]). An alternative approach is through the use of bootstrap methods. This idea was first introduced by Efron ([8]) and later developed in many papers (also in cited above). Bootstrapping of the point processes is not yet fully explored. Some results are presented in [4] and [5]. The Poisson process context is treated in the paper [6],

however these methods cannot be easily adapted to the multiplicative intensity model.

The aim of our work is the construction of the bootstrap simultaneous confidence bands for the Nelson–Aalen estimator. We want to compare constructed bootstrap regions with the asymptotic ones. We make simulations to check if the actual coverage probability is close to a nominal one. In our calculations we use the weird bootstrap method.

We show that for the small samples the bootstrap models have much better coverage probabilities. Not only the actual coverage probabilities of the bootstrap simultaneous confidence bands are very close to nominal ones but also the left- and right-tail error probabilities are almost equal.

Our paper is organized in the following way. Section 2 contains a short survey of basic results related to the Nelson–Aalen estimator and the bootstrap for point processes. Section 3 is dedicated to construction of simultaneous confidence bands for the estimator considered. A practical example related to heart transplant study is included in Section 4, while Section 5 contains additional numerical results. Conclusions and open questions are presented in Section 6.

2 Problem formulation

In our paper we construct the bootstrap simultaneous confidence bands for the integrated intensity function. We use the weird bootstrap introduced in [1]. We compare our results with those presented in [1] and [2]. Application of bootstrap is well motivated in the small sample case and when censoring mechanism is quite complex. Moreover, the standard asymptotic theory provides confidence intervals that are quite difficult to apply. To construct bootstrap simultaneous confidence bands we applied one of the methods proposed in [6].

While defining our problem we follow [1] (page 176). We consider a continuous-time interval \mathcal{T} which may be of the form $[0, \tau]$ or $[0, \tau)$ for a given terminal time τ , $0 < \tau \leq \infty$. Let (Ω, \mathcal{F}) be a measurable space equipped with a filtration $(\mathcal{F}_t, t \in \mathcal{T})$. We define on (Ω, \mathcal{F}) a counting process $\mathbf{N} = (N(t), t \in \mathcal{T})$ adapted to the filtration such that its stochastic intensity function λ is of the form $\lambda(t) = \alpha(t)Y(t)$, where α is nonnegative

deterministic function and Y is a predictable process. For example, we can consider an initial group Y_0 of patients with cancer after some medical treatment. Although the patients enter the study at different calendar times, we observe only their time since operation. In this case $\alpha(t)$ is the individual intensity of death and $Y(t)$ is the number at risk at the moment of time t e.g. number of patients who lived till time t . For a practical example see Section 4.

The only assumption we have to make about α is its integrability,

$$\int_0^t \alpha(s) ds < \infty \quad \text{for all } t \in \mathcal{T}.$$

We consider the Nelson–Aalen estimator \hat{A} for

$$A(t) = \int_0^t \alpha(s) ds$$

which is of the form

$$\hat{A}(t) = \sum_{j: T_j \leq t} \frac{1}{Y(T_j)},$$

where T_j are jump times.

We define an estimator for the mean squared error function as

$$\hat{\sigma}^2(t) = \sum_{j: T_j \leq t} \frac{Y(T_j) - \Delta N(T_j)}{Y^3(T_j)},$$

where $\Delta N(T_j) = N(T_j) - N(T_{j-1})$.

Under the suitable assumptions the Nelson–Aalen estimator is uniformly consistent on compact intervals (see [1] page 190), which means:

$$\sup_{s \in [0, t]} |\hat{A}^{(n)}(s) - A(s)| \xrightarrow{p} 0 \quad \text{as } n \rightarrow \infty \quad \text{for } t \in \mathcal{T}.$$

The asymptotic distribution of the Nelson–Aalen estimator can be obtained from Rebolledo’s martingale central limit theorem (for details see [1] page 190). It should be pointed out that the problem of constructing simultaneous confidence bands requires a version of the functional central limit theorem for the cumulative intensity function. Such results can be found in [1] (page 263), however the limiting distribution is quite difficult to apply in practice. Moreover, it is still unknown what form of the functional central limit theorem can be established for α alone. (See also Section 6 for additional remarks regarding this problem).

The results above can be used to construct pointwise confidence intervals and simultaneous confidence bands for $A(t)$ ([1]). Unfortunately, formulae for the asymptotic distributions are very complicated. That is why we want to apply bootstrap methods to construct simultaneous confidence bands. Bootstrapping of counting processes is not easy because such processes are not based on i.i.d. samples. The problem is complex and, thus, the methods for the general case are not known. There are some results for the Poisson processes (see [6]), however in this case one may get similar results without simulations (see [14]). Some methods of bootstrapping point processes are also presented in [4] and [5].

In our paper we apply the weird bootstrap method. The idea is based on the fact that the asymptotic distribution of $a_n(\hat{A}-A)$ has independent increments and $Var(d\hat{A}(t)|\mathcal{F}_{t-}) = dA(t)(1 - dA(t))/Y(t)$. The following definition is quoted from [1].

Definition 2.1 *The Weird Bootstrap*

Given N , Y , and \hat{A} , let N^ be a process with independent binomial $(Y(t), \Delta\hat{A}(t))$ distributed increments at the jump times of N , constant between jump times. Let $\hat{A}^* = \int dN^*/Y$. Estimate the distribution of $\hat{A} - A$ by the conditional distribution, given N and Y , of $\hat{A}^* - \hat{A}$.*

For the proof of consistency of this method see [1] (page 220).

The word *weird* is not accidental. In every time point $t \in \mathcal{T}$ every individual at risk from the set $Y(t)$ has the same probability of a failure. However, the event at the time t does not exert any influence on any other time moment $s \in \mathcal{T}$.

The problem of bootstrapping point processes is not completely solved and quite challenging. Some partial solution are discussed in [6], [7], [4] and [5]. In the next section we use this method of bootstrapping to construct the simultaneous confidence bands.

3 Simultaneous confidence bands

The Nelson–Aalen point estimator is difficult to interpret without some idea of its accuracy. Resolving this problem requires constructing confidence intervals or confidence bands. These bands are also quite interesting because of their hypothesis testing in-

terpretation. We can think of confidence bands as a one-sample test statistics with a null hypothesis $A = A_0$ which is rejected at significance level θ if A_0 is not completely contained in the band. In this case pointwise confidence intervals are not satisfactory. That is why we introduce simultaneous confidence bands.

Definition 3.1 *Confidence region*

Let \mathcal{B} denote a connected, nonempty, random subset of the rectangle $[0, \tau] \times [0, \infty)$, such that $\mathcal{B} \cap \{(x, y) : 0 \leq y < \infty\}$ is nonempty for each $x \in [0, \tau]$. We call \mathcal{B} a confidence region for A over the set $S \in [0, \tau]$ with a coverage probability $(1 - \theta)$ if $P\{(x, A(x)) \in \mathcal{B} \text{ for all } x \in S\} = \theta$.

In our paper S is always an interval.

Simultaneous confidence bands may be constructed in many different ways. The authors of the book [1] (page 209) proposed two types of such bands: EP-band (equal precision band) and HW-band (Hall–Wellner band). These confidence bands are based on the asymptotic distribution of the Nelson–Aalen estimator on compact intervals which can be derived from the martingale central limit theorem.

Both EP- and HW-band for A on $[t_1, t_2]$ are of the form

$$\hat{A}(s) \pm a_n^{-1} K_{q,\theta}(c_1, c_2) (1 + a_n^2 \hat{\sigma}^2(s)) / q \left(\frac{a_n^2 \hat{\sigma}^2(s)}{1 + a_n^2 \hat{\sigma}^2(s)} \right)$$

with $K_{q,\theta}(c_1, c_2)$ being the upper percentile of the distribution of

$$\sup_{x \in [c_1, c_2]} |q(x) W^0(x)|,$$

where W^0 denotes the standard Brownian bridge.

The constants c_1 and c_2 can be approximated by

$$\hat{c}_i = \frac{a_n^2 \hat{\sigma}^2(t_i)}{1 + a_n^2 \hat{\sigma}^2(t_i)},$$

where $a_n = \sqrt{n}$ is a normalizing factor and n is the number of individuals at study. For EP-band q is chosen as $q_1(x) = \{x(1 - x)\}^{-1/2}$ which yields the confidence bands proportional to the pointwise ones. For HW-band q is chosen as $q_2(x) = 1$. In both cases θ percentile of the asymptotic distribution are difficult to obtain. These bands also perform badly even with the sample size of 100–200 [2]. Because of this reason one may consider some transformations to improve the approximation to the

asymptotic distribution [1] (page 211).

To avoid such problems we consider bootstrap simultaneous confidence bands. The authors of the paper [6] proposed a few different methods of constructing these bands. In our calculations we use the weird bootstrap method. Our construction of bootstrap-t confidence regions for A is based on the bootstrap approximation

$$T^*(x) = \frac{\hat{A}^*(x) - \hat{A}(x)}{\hat{\sigma}(x)}, \quad x \in \mathcal{T}$$

of

$$T(x) = \frac{\hat{A}(x) - A(x)}{\hat{\sigma}(x)}, \quad x \in \mathcal{T}.$$

For details see [1].

Below we present two bootstrap confidence bands:

1. Confidence region is defined by

$$\mathcal{B}_1 = \{(x, y) : x \in S, \max[0, \hat{A}(x) - t_1 \hat{\sigma}(x)] \leq y \leq \hat{A}(x) + t_1 \hat{\sigma}(x)\},$$

where t_1 is chosen such that

$$P\{|T^*(x)| \leq t_1, \text{ all } x \in S | N, Y\} = 1 - \theta.$$

The main feature of this region is that at the point x its width is proportional to $\hat{\sigma}(x)$.

2. In many applications populations cannot be modelled via symmetric distributions. The only reasonable choice is a strongly skewed distribution. In all of the previous presented intervals, skewness was not taken into consideration. This has a quite negative impact on the coverage probability. To adjust for skewness of the distribution one could construct a region which the left- and right-tail error probabilities are equal. This kind of the region is of the form

$$\mathcal{B}_2 = \{(x, y) : x \in S, \max[0, \hat{A}(x) - t_3 \hat{\sigma}(x)] \leq y \leq \hat{A}(x) - t_2 \hat{\sigma}(x)\},$$

where t_2 and t_3 are chosen such that

$$P\{t_2 \leq T^*(x) \leq t_3, \text{ all } x \in S | N, Y\} = 1 - \theta$$

and

$$P\{T^*(x) \leq t_2, \text{ all } x \in S|N, Y\} = P\{T^*(x) \geq t_3, \text{ all } x \in S|N, Y\}.$$

In the next section we present an example of applying such bands.

4 Practical example

We take under the consideration the group of 64 patients after heart transplant. The data we use are taken from [9], Appendix A, pages 387-389. In our approach, the risk is defined as the rejection of the transplant so the time between the operation and the rejection is considered. 35 observations are censored. The censoring was present if patients were alive at the end of the study or lost to follow-up. The 95% confidence bands simultaneous with respect to the time argument were constructed in the time bandwidth between day 20 and day 1200 of the observation. The construction of such confidence interval was based on Nelson–Aalen estimator. Figure 1 presents the Nelson–Aalen estimator together with HW and EP bands and Figure 2 with $\mathcal{B}1$ and $\mathcal{B}2$ bootstrap simultaneous confidence bands. Note that $\mathcal{B}1$, EP and HW bands are symmetric. Only $\mathcal{B}2$ is not symmetric. The upper bands of $\mathcal{B}1$ and $\mathcal{B}2$ are covering themselves. The lower band of $\mathcal{B}1$ is noticeably too low. It suggests that $\mathcal{B}1$ is too wide. HW and EP bands are close to each other but EP is significantly broader during the most part of the time interval. Moreover, $\mathcal{B}2$ is shifted upwards compared with the asymptotic simultaneous confidence bands.

Now we will verify the actual coverage probability for the considered bands.

5 Numerical results

Our aim is to compare the coverage probability for asymptotic and bootstrap simultaneous confidence bands. Our simulations are based on the multiplicative model for the intensity function $\lambda(t) = Y(t)\alpha(t)$. We concentrate on a few typical examples of the α function. To generate process Y we first choose the beginning value Y_0 (the number of individuals at risk) and next for every individual the time of termination is sampled from exponential distribution with the mean value 0.25. Having such Y we generate the underlying point process.

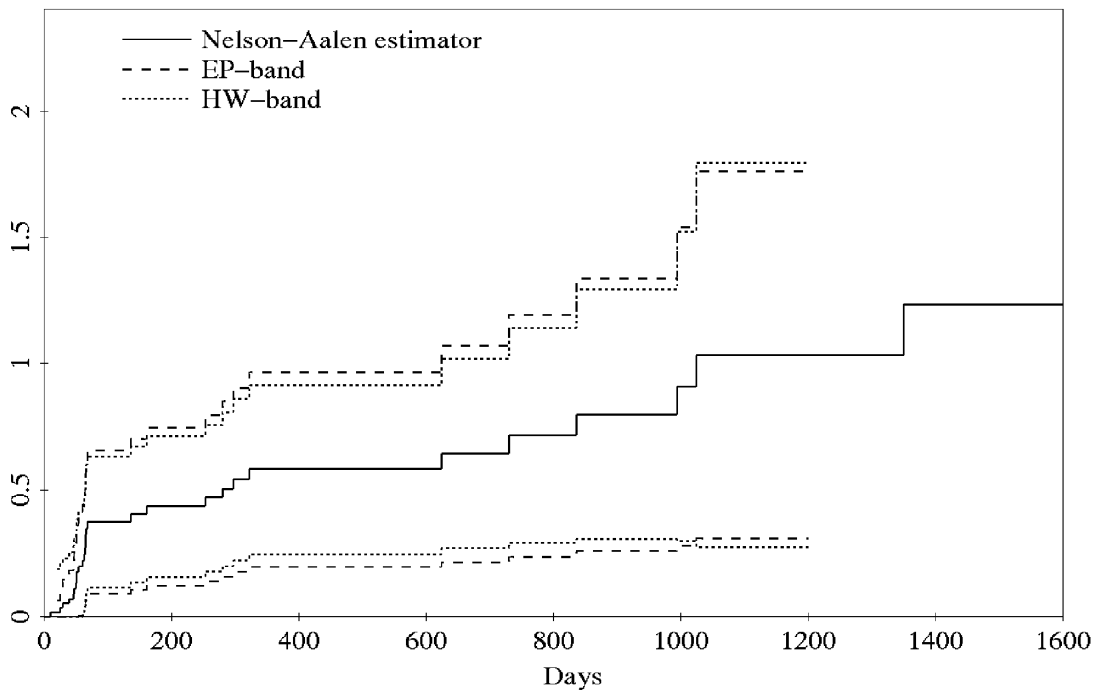


Figure 1: HW- and EP-band

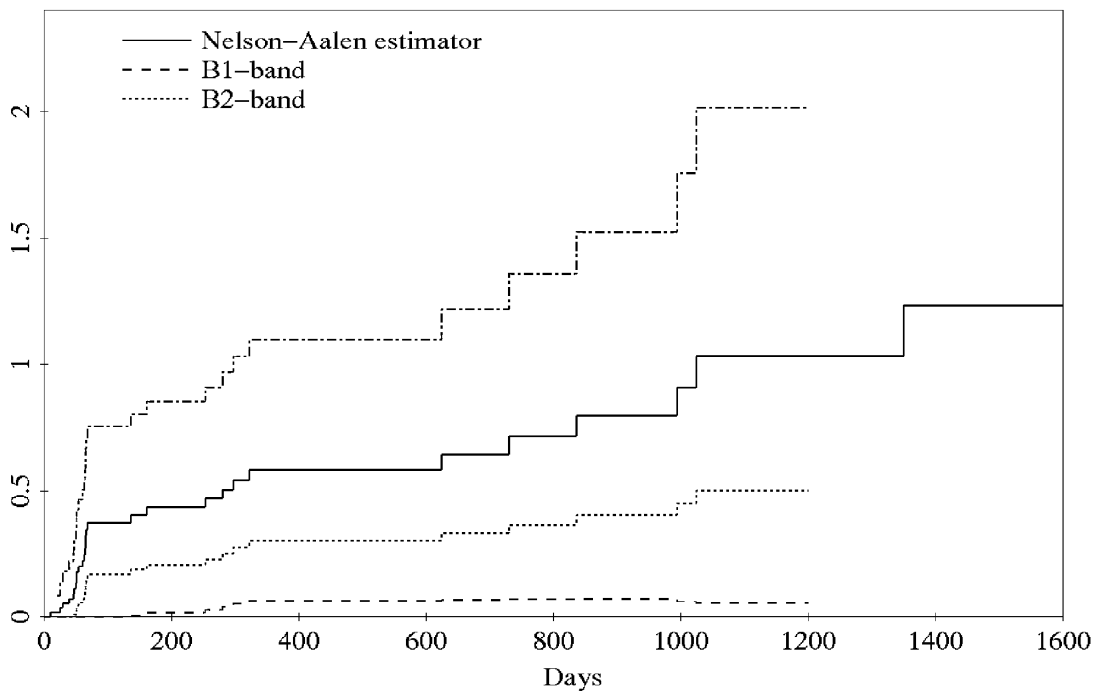


Figure 2: $\mathcal{B}1$ - and $\mathcal{B}2$ -band

For our study we chose four functions:

$$\begin{aligned}\alpha_1(t) &= \frac{5}{3}, \\ \alpha_2(t) &= \frac{5}{6} + 10(t - 0.5)^2, \\ \alpha_3(t) &= \frac{5}{3} + 10(t - 0.5)^3, \\ \alpha_4(t) &= 2.5 - 10(t - 0.5)^2.\end{aligned}$$

Curves of such kinds can be applied in biomedicine, insurance and demography. For example the U-shaped functions may reflect behavior of the intensity of death and the inverted U-shaped functions may describe the intensity of birth. These shapes are reflected in the equation of α_2 and α_4 functions. Figure 3 shows these intensity functions and Figure 4 presents integrated versions of these functions.

We make simulations for the interval $S = [0.2; 0.8]$, the number of bootstrap resamples $B = 200$ and initial number at risk $Y_0 : 25, 50, 75$. In Table 1 we show the actual coverage probability, when the nominal coverage probability is 0.95 and the number of iterations is equal to 10000. For every Y_0 , α_i function ($i = 1 \dots 4$) and method of construction of the confidence region, the first and the second number in Table 1 are the left- and right-tail error probabilities and the third is the actual coverage probability (all probabilities are measured in percentage).

As we expected, HW- and EP-band perform quite badly for the small samples. Especially for $Y_0 = 25$ the actual coverage probability is 5% to 10% less than it should be. This happens because these are asymptotic bands and in our case the number of jumps of the point processes is not big enough to apply the asymptotic distribution. For $Y_0 = 50$ the actual coverage probability for these bands is better but always remains about 3% smaller than the nominal one. For $Y_0 = 75$ all results are satisfactory. The first of the bootstrap confidence intervals which we proposed performs well for small Y_0 but when the number of jumps rises it remains consistently too wide. The equal-tailed bootstrap confidence band ($\mathcal{B}2$) behaves well in all considered situations. Its actual coverage probability is always close to nominal, even in the case of small beginning number at risk (when the asymptotic bands fail). Our simulations also show that the left-side failure probability for the EP- and HW-band is significantly too small. Its value is below 1%. This means that our functions $\alpha_i(t)$ almost never cross the lower band of the confidence region e.g. the lower band goes too far away from the estima-

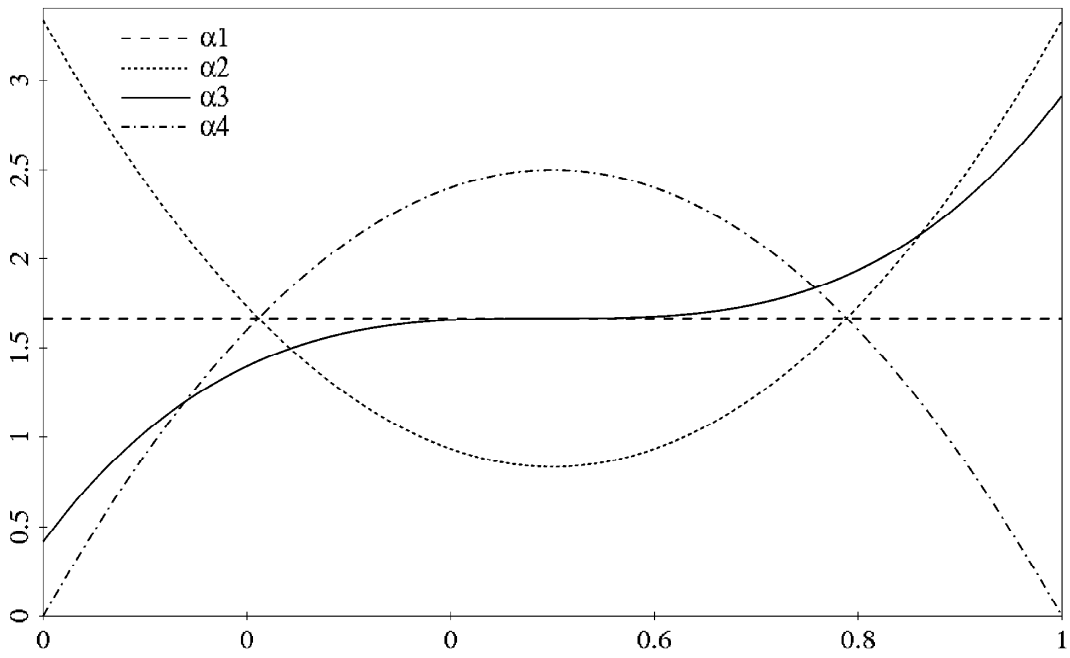


Figure 3: Intensity functions

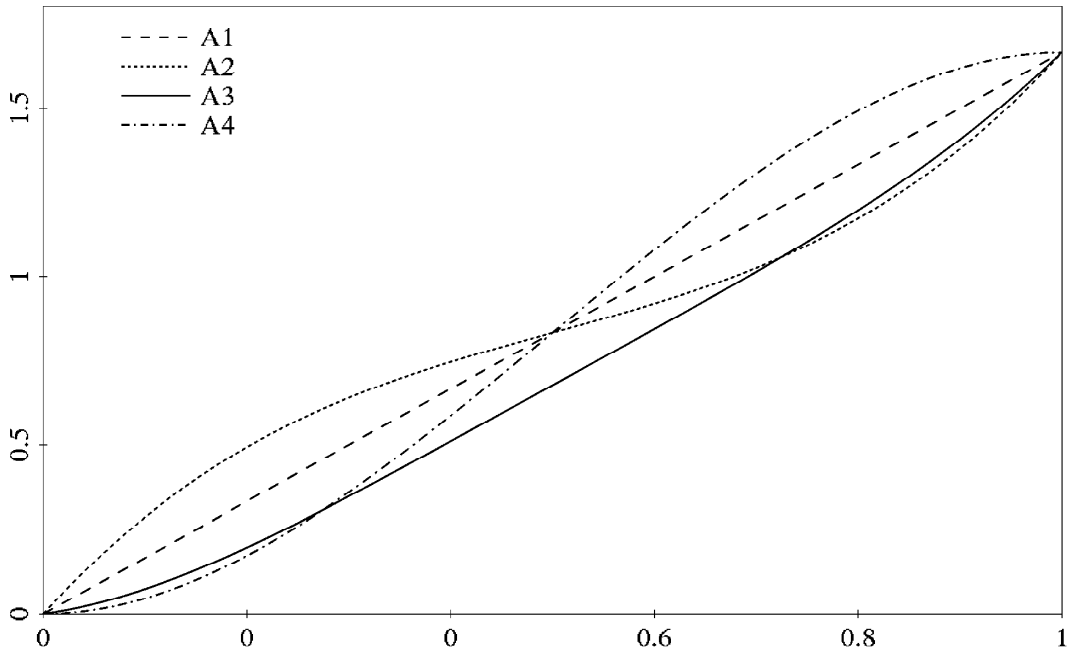


Figure 4: Integrated intensity functions

		Y_0								
function	method	25			50			75		
α_1	HW	0.4	11.5	88.1	0.6	5.7	93.7	0.8	4.1	95.1
	EP	0.4	12.7	87.0	0.6	6.6	92.8	0.8	4.7	94.5
	$\mathcal{B}1$	0.0	4.0	96.0	0.1	2.5	97.4	0.3	2.2	97.5
	$\mathcal{B}2$	2.4	4.0	93.6	3.2	2.6	94.3	3.1	2.2	94.7
α_2	HW	0.5	10.1	89.5	0.9	6.5	92.7	1.0	4.7	94.3
	EP	0.5	10.0	89.5	0.8	6.6	92.6	1.0	5.0	94.1
	$\mathcal{B}1$	0.1	3.6	96.3	0.2	3.4	96.4	0.3	2.6	97.1
	$\mathcal{B}2$	2.6	3.6	93.8	3.0	3.6	93.4	3.1	2.9	94.1
α_3	HW	0.2	13.2	86.6	0.7	9.8	89.5	0.8	4.7	94.5
	EP	0.2	14.8	85.0	0.5	9.4	90.1	0.7	5.6	93.7
	$\mathcal{B}1$	0.0	4.7	95.3	0.9	2.9	96.3	0.1	1.6	98.3
	$\mathcal{B}2$	2.3	4.7	93.0	2.9	2.2	95.0	2.9	1.7	95.5
α_4	HW	0.7	13.8	85.8	0.5	6.7	92.8	0.9	4.4	94.8
	EP	1.0	16.6	83.1	0.3	8.5	91.2	0.8	5.3	93.9
	$\mathcal{B}1$	1.0	5.2	94.7	0.1	2.3	97.6	0.1	1.5	98.4
	$\mathcal{B}2$	2.6	5.1	92.5	2.7	2.3	95.0	3.3	1.5	95.2

Table 1: Actual coverage probability

tor. The advantage of the $\mathcal{B}2$ region is the equal tailed feature. The lack of coverage probabilities for the left-hand case and the right-hand case are almost equal.

We checked empirically that $\mathcal{B}2$ is the optimal choice. Independently of the beginning number at risk it has a coverage probability close to the nominal one and, what is very important, it insures almost equally divided failure probability.

Now we compare our results with those presented in [2]. The authors of [2] proposed arcsine- and logarithmic-transform of the Nelson-Aalen estimator. They considered the modifications of EP- and HW-band which use these transformations. Such constructed asymptotic simultaneous confidence bands perform satisfactory for sample size as low as 25.

Using simulation methods presented before we compare the behaviour of these bands to the bootstrap band $\mathcal{B}2$. The results are presented in Table 2. AHW and AEP denote

the arcsine-transform of HW- and EP-band respectively. The logarithmic-transform bands are denoted by LHW and LEP.

As might be expected for the sample size 50 and 75 all methods give satisfactory

function	method	Y_0								
		25			50			75		
α_1	AHW	2.2	6.6	91.2	2.7	3.1	94.2	2.7	2.0	95.3
	AEP	2.3	5.9	91.8	2.6	3.3	94.1	2.7	2.0	95.3
	LHW	3.1	5.1	91.8	3.5	2.4	94.1	3.4	1.4	95.2
	LEP	3.2	3.8	93.0	3.4	2.0	94.6	3.3	1.3	95.4
	$\mathcal{B}2$	2.4	4.0	93.6	3.2	2.6	94.3	3.1	2.2	94.7
α_2	AHW	2.3	4.8	92.9	2.4	3.2	94.4	2.4	2.2	95.4
	AEP	2.3	4.5	93.2	2.3	3.3	94.4	2.4	2.3	95.3
	LHW	3.0	3.2	93.8	3.0	2.4	94.6	2.9	1.6	95.5
	LEP	3.1	2.4	94.5	2.9	2.0	95.1	3.0	1.5	95.5
	$\mathcal{B}2$	2.6	3.6	93.8	3.0	3.6	93.4	3.1	2.9	94.1
α_3	AHW	2.3	8.7	89.0	2.5	3.8	93.7	2.4	2.3	95.3
	AEP	2.2	6.6	91.2	2.2	3.1	94.7	2.3	2.3	95.4
	LHW	3.8	6.2	90.0	3.5	2.8	93.7	3.6	1.8	94.6
	LEP	3.8	4.5	91.7	3.5	1.8	94.7	3.6	1.1	95.3
	$\mathcal{B}2$	2.3	4.7	93.0	2.9	2.2	95.0	2.9	1.7	95.5
α_4	AHW	2.3	8.8	88.9	2.5	3.0	94.5	2.5	2.3	95.2
	AEP	2.3	7.3	90.4	2.3	3.1	94.6	2.4	2.1	95.5
	LHW	4.0	7.4	88.6	3.9	2.5	93.4	3.5	1.6	94.9
	LEP	3.6	5.7	90.7	3.6	1.7	94.7	3.3	1.1	95.6
	$\mathcal{B}2$	2.6	5.1	92.5	2.7	2.3	95.0	3.3	1.5	95.2

Table 2: Actual coverage probability

results. For a sample size 25 the bootstrap simultaneous confidence band $\mathcal{B}2$ has better coverage properties than transformed asymptotic ones. The actual coverage probability of $\mathcal{B}2$ is about 92.5% for all α_i functions. It is about 2% closer to the nominal than the actual coverage probability of the transformed bands. At first sight LEP seems to be good choice but as the sample size grows it gets too wide.

However, considered transformations improve the actual coverage probability and the left- and right-tail error probabilities of the asymptotic bands \mathcal{B}_2 is still the best choice.

6 Conclusions

In many applications, the hazard function is much more interesting and relevant to estimate than the integrated hazard function, but it is also more challenging to estimate. There are several approaches to that problem, the histogram based sieve estimator considered in Leśkow, Róžański [11] and Leśkow [10] being one of them. Unfortunately, the version of functional central limit theorem of such estimator is still an open question. Without such result construction of the simultaneous confidence bands is impossible.

In our paper we showed that for the small samples the bootstrap simultaneous confidence bands behave better than the asymptotic ones. They also have better actual coverage probability. An advantage of the equal-tailed type confidence region is the balance of the left- and right-tail error probability. A disadvantage of all simultaneous regions considered in this paper is the lack of taking into a consideration the shape of the estimated function. The integrated hazard function is always nondecreasing. Unfortunately, the lower confidence band decreases sometimes. It may be interesting to construct regions taking into consideration the known features of the estimated function (for example monotonicity, unimodality).

The other curious problem is bootstrapping of the point process. We consider only one method (the weird bootstrap). In the paper [6] other methods are proposed but only for Poisson processes. A method for obtaining bootstrap replicates for the one-dimensional point process is presented in [4] and its multi-dimensional version is also proposed. Because of deficient coverage properties in some cases, Braun and Kulperger proposed in [5] a technique for one-dimensional point process which uses the idea of re-colouring presented in [7]. It remains an open question if these methods can be applied in a general case.

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